



INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁵ : C07D 453/02, A61K 31/435		A1	(11) International Publication Number: WO 92/21677
			(43) International Publication Date: 10 December 1992 (10.12.92)

<p>(21) International Application Number: PCT/US92/03317</p> <p>(22) International Filing Date: 28 April 1992 (28.04.92)</p> <p>(30) Priority data: 708,404 31 May 1991 (31.05.91) US</p> <p>(60) Parent Application or Grant (63) Related by Continuation US 708,404 (CIP) Filed on 31 May 1991 (31.05.91)</p> <p>(71) Applicant (for all designated States except US): PFIZER INC. [US/US]; 235 East 42nd Street, New York, NY 10017 (US).</p> <p>(72) Inventors; and (75) Inventors/Applicants (for US only) : ITO, Fumitaka; 1-1-2, Sakuragaoka, Taketoyo-cho, Chita 470-23 (JP). KONDO, Hiroshi [JP/JP]; 2-1 cho, Handa, Aichi 475 (JP). SHIMADA, Kaoru; 171, Dannoue, Iwadzo-cho, Okazaki, Aichi 466 (JP). ITO, Masami [JP/JP]; 6-28-203, Kashi, Showa-ku, Nagoya-shi, Aichi 466 (JP). I. Adams, III [US/US]; 28 Coveside Lane, Str 06378 (US). ROSEN, Terry, Jay [US/US]; Hill Road, East Lyme, CT 06333 (US). YAN Vera [CN/US]; 27 Lincoln Road, Waterfor (US).</p>	<p>(74) Agents: RICHARDSON, Peter, C. et al.; Pfizer Inc., 235 East 42nd Street, New York, NY 10017 (US).</p> <p>(81) Designated States: AT (European patent), AU, BE (European patent), BF (OAPI patent), BG, BJ (OAPI patent), BR, CA, CF (OAPI patent), CG (OAPI patent), CH (European patent), CI (OAPI patent), CM (OAPI patent), CS, DE (Utility model), DE (European patent), DK (European patent), ES (European patent), FI, FR (European patent), GA (OAPI patent), GB (European patent), GN (OAPI patent), GR (European patent), HU, IT (European patent), JP, KR, LU (European patent), MC (European patent), ML (OAPI patent), MR (OAPI patent), NL (European patent), NO, PL, RO, RU, SE (European patent), SN (OAPI patent), TD (OAPI patent), TG (OAPI patent), US.</p>
---	--

39

I search report.
tion of the time limit for amending the
epublished in the event of the receipt of

(54) Title: QUINUCLIDINE DERIVATIVES

(I)

(57) Abstract

Compounds of formula (I), wherein R¹ is methoxy and R² is selected from the group consisting of methyl, ethyl, isopropyl, sec-butyl and tert-butyl; and the pharmaceutically acceptable salts of such compounds. These compounds are substance P antagonists and useful in the treatment of gastrointestinal disorders, inflammatory disorders, central nervous system disorders and pain.

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AT	Austria	FI	Finland	MI	Mali
AU	Australia	FR	France	MN	Mongolia
BB	Barbados	GA	Gabon	MR	Mauritania
BE	Belgium	GB	United Kingdom	MW	Malawi
BF	Burkina Faso	GN	Guinea	NL	Netherlands
BG	Bulgaria	GR	Greece	NO	Norway
BJ	Benin	HU	Hungary	PL	Poland
BR	Brazil	IE	Ireland	RO	Romania
CA	Canada	IT	Italy	RU	Russian Federation
CF	Central African Republic	JP	Japan	SD	Sudan
CG	Congo	KP	Democratic People's Republic of Korea	SE	Sweden
CH	Switzerland	KR	Republic of Korea	SN	Senegal
CI	Côte d'Ivoire	LI	Liechtenstein	SU	Soviet Union
CM	Cameroon	LK	Sri Lanka	TD	Chad
CS	Czechoslovakia	LU	Luxembourg	TC	Togo
DE	Germany	MC	Monaco	US	United States of America
DK	Denmark	MG	Madagascar		
ES	Spain				

-1-

5

QUINUCLIDINE DERIVATIVESBackground of the Invention

The present invention relates to novel quinuclidine derivatives, pharmaceutical compositions comprising such compounds and the use of such compounds in the treatment and prevention of inflammatory and central nervous system disorders, as well as several other disorders. The pharmaceutically active compounds of this invention are substance P receptor antagonists. This invention also relates to novel intermediates used in the synthesis of such substance P antagonists.

Substance P is a naturally occurring undecapeptide belonging to the tachykinin family of peptides, the latter being named because of their prompt stimulatory action on smooth muscle tissue. More specifically, substance P is a pharmacologically active neuropeptide that is produced in mammals (having originally been isolated from gut) and possesses a characteristic amino acid sequence that is illustrated by D. F. Veber et al. in U.S. Patent No. 4,680,283. The wide involvement of substance P and other tachykinins in the pathophysiology of numerous diseases has been amply demonstrated in the art. For instance, substance P has recently been shown to be involved in the transmission of pain or migraine (see B.E.B. Sandberg et al., Journal of Medicinal Chemistry, 25, 1009 (1982)), as well as in central nervous system disorders such as anxiety and schizophrenia, in respiratory and inflammatory diseases such as asthma and rheumatoid arthritis, respectively, in rheumatic diseases such as fibrositis, and in gastrointestinal disorders and diseases of the GI tract such as ulcerative colitis and Crohn's disease, etc. (see D. Regoli in "Trends in Cluster Headache," edited by F. Sicuteri et al., Elsevier Scientific Publishers, Amsterdam, pp. 85-95 (1987)).

In the recent past, some attempts have been made to provide antagonists for substance P and other tachykinin peptides in order to more effectively treat the various disorders and diseases listed above. The few such

-2-

antagonists thus far described are generally peptide-like in nature and are therefore too labile from a metabolic point of view to serve as practical therapeutic agents in the treatment of disease. The non-peptidic antagonists of the present invention, on the other hand, do not possess this drawback, being far more stable from a metabolic point of view than the agents referred to above.

The quinuclidine derivatives of this invention are referred to generically in PCT Patent Application PCT/US 89/05338, filed November 20, 1989 and United States Patent Application Serial No. 557,442, filed July 23, 1990, both of which are assigned in common with the present application. Other quinuclidine derivatives that exhibit activity as substance P receptor antagonists are referred to in PCT patent application PCT/US 91/02853, entitled "3-Amino-2-Aryl Quinuclidines" and filed on April 25, 1991 and in PCT patent application PCT/US 92/03369, entitled "Quinuclidine Derivatives" and filed on May 14, 1991. These applications are also assigned in common with the present application.

Piperidine derivatives and related heterocyclic nitrogen containing compounds that are useful as substance P antagonists are referred to in United States Patent Application Serial No. 619,361, filed November 28, 1990 and United States Patent Application Serial No. 590,423, filed September 28, 1990, both of which are assigned in common with the present application.

Summary of the Invention

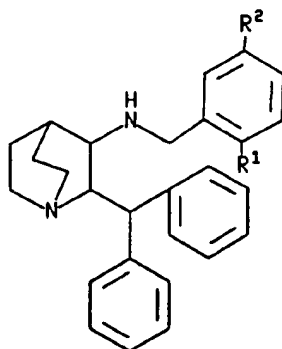
The present invention relates to compounds of the formula

30

35

-3-

5



10 wherein R¹ is methoxy and R² is independently selected from the group consisting of isopropyl, tert-butyl, methyl, ethyl and sec-butyl; and the pharmaceutically acceptable salts of such compounds.

Specific compounds of this invention include the
15 following:

(2S,3S)-N-(5-isopropyl-2-methoxyphenyl)methyl-2-diphenylmethyl-1-azabicyclo[2.2.2]octan-3-amine;

(2S,3S)-N-(5-tert-butyl-2-methoxyphenyl)methyl-2-diphenylmethyl-1-azabicyclo[2.2.2]octan-3-amine;

20 (2S,3S)-N-(5-methyl-2-methoxyphenyl)methyl-2-diphenylmethyl-1-azabicyclo[2.2.2]octan-3-amine;

(2S,3S)-N-(5-ethyl-2-methoxyphenyl)methyl-2-diphenylmethyl-1-azabicyclo[2.2.2]octan-3-amine;

(2S,3S)-N-(5-isopropyl-2-methoxyphenyl)methyl-2-
25 diphenylmethyl-1-azabicyclo[2.2.2]octan-3-amine;

(2S,3S)-N-(5-sec-butyl-2-methoxyphenyl)methyl-2-diphenylmethyl-1-azabicyclo[2.2.2]octan-3-amine;

and the pharmaceutically acceptable salts of such compounds.

30 The present invention also relates to a pharmaceutical composition for treating or preventing a condition selected from the group consisting of inflammatory diseases (e.g., arthritis, psoriasis, asthma and inflammatory bowel disease), anxiety, depression or dysthymic disorders,
35 colitis, psychosis, pain, allergies such as eczema and rhinitis, chronic obstructive airways disease, hypersensitivity disorders such as poison ivy, hypertension,

-4-

vasospastic diseases such as angina, migraine and Reynaud's disease, fibrosing and collagen diseases such as scleroderma and eosinophilic fascioliasis, reflex sympathetic dystrophy such as shoulder/hand syndrome, addiction disorders such as
5 alcoholism, stress related somatic disorders, peripheral neuropathy, neuralgia, neuropathological disorders such as Alzheimer's disease, AIDS related dementia, diabetic neuropathy and multiple sclerosis, disorders related to immune enhancement or suppression such as systemic lupus
10 erythematosus, and rheumatic diseases such as fibrositis in a mammal, including a human, comprising an amount of a compound of the formula I, or a pharmaceutically acceptable salt thereof, effective in treating or preventing such condition, and a pharmaceutically acceptable carrier.

15 The present invention also relates to a method of treating or preventing a condition selected from the group consisting of inflammatory diseases (e.g., arthritis, psoriasis, asthma and inflammatory bowel disease), anxiety, depression or dysthymic disorders, colitis, psychosis, pain,
20 allergies such as eczema and rhinitis, chronic obstructive airways disease, hypersensitivity disorders such as poison ivy, hypertension, vasospastic diseases such as angina, migraine and Reynaud's disease, fibrosing and collagen diseases such as scleroderma and eosinophilic fascioliasis,
25 reflex sympathetic dystrophy such as shoulder/hand syndrome, addiction disorders such as alcoholism, stress related somatic disorders, peripheral neuropathy, neuralgia, neuropathological disorders such as Alzheimer's disease, AIDS related dementia, diabetic neuropathy and multiple
30 sclerosis, disorders related to immune enhancement or suppression such as systemic lupus erythematosus, and rheumatic diseases such as fibrositis in a mammal, including a human, comprising administering to said mammal an amount
35 acceptable salt thereof, effective in treating or preventing such condition.

-5-

The present invention also relates to a pharmaceutical composition for antagonizing the effects of substance P in a mammal, including a human, comprising a substance P antagonizing amount of a compound of formula I, or a
5 pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

The present invention also relates to a method of antagonizing the effects of substance P in a mammal, including a human, comprising administering to said mammal
10 a substance P antagonizing amount of a compound of formula I or a pharmaceutically acceptable salt thereof.

The present invention also relates to a pharmaceutical composition for treating or preventing a disorder in a mammal, including a human, resulting from an excess of
15 substance P, comprising a substance P antagonizing amount of a compound of formula I, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

The present invention also relates to a method of treating or preventing a disorder in a mammal, including a
20 human, resulting from an excess of substance P, comprising administering to said mammal a substance P antagonizing amount of a compound of the formula I, or a pharmaceutically acceptable salt thereof.

The present invention also relates to a pharmaceutical
25 composition for treating or preventing a condition selected from the group consisting of inflammatory diseases (e.g., arthritis, psoriasis, asthma and inflammatory bowel disease), anxiety, depression or dysthymic disorders, colitis, psychosis, pain, allergies such as eczema and
30 rhinitis, chronic obstructive airways disease, hypersensitivity disorders such as poison ivy, hypertension, vasospastic diseases such as angina, migraine and Reynaud's disease, fibrosing and collagen diseases such as scleroderma and eosinophilic fascioliasis, reflex sympathetic dystrophy
35 such as shoulder/hand syndrome, addiction disorders such as alcoholism, stress related somatic disorders, peripheral neuropathy, neuralgia, neuropathological disorders such as

-6-

Alzheimer's disease, AIDS related dementia, diabetic neuropathy and multiple sclerosis, disorders related to immune enhancement or suppression such as systemic lupus erythematosus, and rheumatic diseases such as fibrositis in a mammal, including a human, comprising an amount of a compound of the formula I, or a pharmaceutically acceptable salt thereof, effective in antagonizing the effect of substance P at its receptor site, and a pharmaceutically acceptable carrier.

10 The present invention also relates to a method of treating or preventing a condition selected from the group consisting of inflammatory diseases (e.g., arthritis, psoriasis, asthma and inflammatory bowel disease), anxiety, depression or dysthymic disorders, colitis, psychosis, pain, 15 allergies such as eczema and rhinitis, chronic obstructive airways disease, hypersensitivity disorders such as poison ivy, hypertension, vasospastic diseases such as angina, migraine and Reynaud's disease, fibrosing and collagen diseases such as scleroderma and eosinophilic fascioliasis, 20 reflex sympathetic dystrophy such as shoulder/hand syndrome, addiction disorders such as alcoholism, stress related somatic disorders, peripheral neuropathy, neuralgia, neuropathological disorders such as Alzheimer's disease, AIDS related dementia, diabetic neuropathy and multiple 25 sclerosis, disorders related to immune enhancement or suppression such as systemic lupus erythematosus, and rheumatic diseases such as fibrositis in a mammal, including a human, comprising administering to said mammal an amount of a compound of the formula I, or a pharmaceutically 30 acceptable salt thereof, effective in antagonizing the effect of substance P at its receptor site.

The present invention also relates to a pharmaceutical composition for treating or preventing a disorder in a mammal, including a human, the treatment or prevention of 35 which is effected or facilitated by a decrease in substance P mediated neurotransmission, comprising an amount of a compound of the formula I, or a pharmaceutically acceptable

-7-

salt thereof, effective in antagonizing the effect of substance P at its receptor site, and a pharmaceutically acceptable carrier.

The present invention also relates to a method of treating or preventing a disorder in mammal, including a human, the treatment or prevention of which is effected or facilitated by a decrease in substance P mediated neurotransmission, comprising administering to said mammal an amount of a compound of the formula I, or a pharmaceutically acceptable salt thereof, effective in antagonizing the effect of substance P at its receptor site.

The present invention also relates to a pharmaceutical composition for treating or preventing a disorder in a mammal, including a human, the treatment or prevention of which is effected or facilitated by a decrease in substance P mediated neurotransmission, comprising an amount of a compound of the formula I, or a pharmaceutically acceptable salt thereof, effective in treating or preventing such disorder, and a pharmaceutically acceptable carrier.

The present invention also relates to a method of treating or preventing a disorder in mammal, including a human, the treatment or prevention of which is effected or facilitated by a decrease in substance P mediated neurotransmission, comprising administering to said mammal an amount of a compound of the formula I, or a pharmaceutically acceptable salt thereof, effective in treating or preventing such disorder.

The compounds of this invention, have chiral centers and therefore exist in different enantiomeric forms. This invention relates to all optical isomers and all stereoisomers of compounds of the formula I, and mixtures thereof.

The compounds of this invention include compounds identical to those described above but for the fact that one or more hydrogen, nitrogen or carbon atoms are replaced by isotopes thereof (e.g., tritium or carbon-14 isotopes). Such compounds are useful as research and diagnostic tools

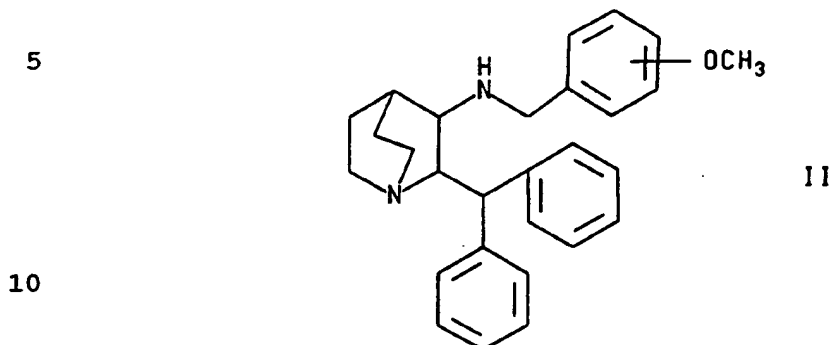
-8-

in metabolism pharmokinetic studies and in binding assays. Specific applications in research include radioligand binding assays, autoradiography studies and in vivo binding studies, while specific applications in the diagnostic area
5 include studies of the substance P receptor in the human brain in in vivo binding in the relevant tissues for inflammation, e.g. immune-type cells or cells that are directly involved in inflammatory bowel disorders and the like.

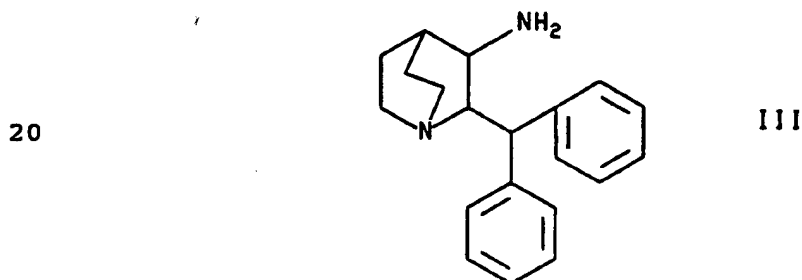
-9-

Detailed Description of the Invention

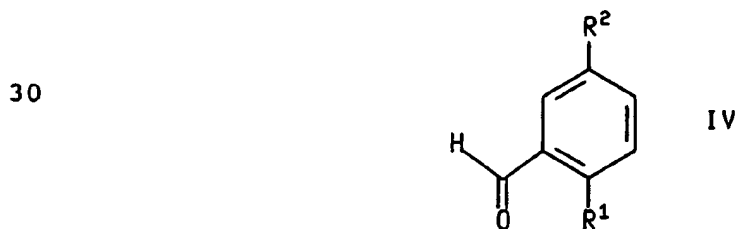
The compounds of this invention may be prepared by
subjecting a compound of the formula



having the same absolute stereochemistry as the desired
compound of formula I, to hydrolytic removal of the
15 methoxybenzyl group to produce the corresponding compound of
the formula



25 having the same stereochemistry, and then reacting the
compound of formula III so formed with an aldehyde of the
formula



35 in the presence of a reducing agent.

Hydrolytic removal of the methoxybenzyl group is
generally carried out using a strong mineral acid such as

-10-

hydrochloric, hydrobromic or hydroiodic acid, at a temperature from about room temperature to about the reflux temperature of the acid. Preferably, the reaction is conducted in hydrobromic acid at the reflux temperature.

5 This reaction is usually carried out for a period of about 2 hours.

Alternatively, the hydrolytic removal of the methoxybenzyl group in the above procedure may be replaced by hydrogenolytic removal of such group. Hydrogenolytic

10 removal is generally accomplished using hydrogen in the presence of a metal containing catalyst such as platinum or palladium. This reaction is usually conducted in a reaction inert solvent such as acetic acid or a lower alcohol, at a temperature from about 0°C to about 50°C. The methoxybenzyl

15 group may also be removed, alternatively, by treating the compound of formula II with a dissolving metal such as lithium or sodium in ammonia at a temperature from about -30°C to about 78°C, or with a formate salt in the presence of palladium or with cyclohexane in the presence of

20 palladium.

Preferably, the methoxybenzyl group is removed by treating the compound of formula II with hydrogen in the presence of palladium hydroxide on carbon in methanol containing hydrochloric acid at a temperature of about 25°C.

25 The resulting compound of formula III may be converted into the desired compound of formula I by reaction with the appropriate aldehyde of formula IV in the presence of a reducing agent. The reaction is typically carried out using a reducing agent such as sodium cyanoborohydride, sodium

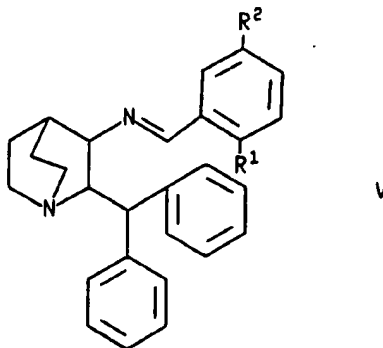
30 triacetoxymethylborohydride, sodium borohydride, hydrogen and a metal catalyst, zinc and hydrochloric acid, borane dimethylsulfide or formic acid at a temperature from about -60°C to about 50°C. Suitable reaction inert solvents for this reaction include lower alcohols (e.g., methanol,

35 ethanol and isopropanol), acetic acid, methylene chloride and tetrahydrofuran (THF). Preferably, the solvent is methylene chloride, the temperature is about 25°C, and the

-11-

reducing agent is sodium triacetoxyborohydride.

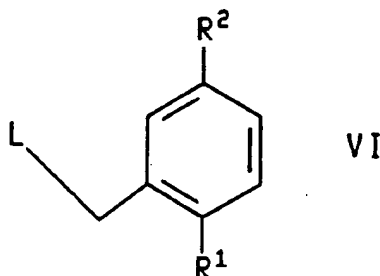
Alternatively, the reaction of a compound of the formula III with a compound of the formula IV may be carried out in the presence of a drying agent or using an apparatus
5 designed to remove azeotropically the water generated, to produce an imine of the formula



15

which is then reacted with a reducing agent as described above, preferably with sodium triacetoxyborohydride at about room temperature. The preparation of the imine is generally carried out in a reaction inert solvent such as benzene,
20 xylene or toluene, preferably toluene, at a temperature from about 25°C to about 110°C, preferably at about the reflux temperature of the solvent. Suitable drying agents/solvent systems include titanium tetrachloride/dichloromethane, titanium isopropoxide/dichloromethane and molecular
25 sieves/THF. Titanium tetrachloride/dichloromethane is preferred.

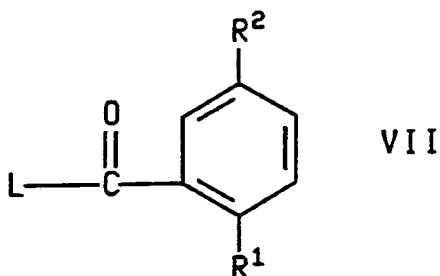
Compounds of the formula III may also be converted into compounds of the formula I having the same stereochemistry by reaction with the appropriate compound of the formula



-12-

wherein L is a leaving group (e.g., chloro, bromo, iodo or mesylate). This reaction is generally carried out in a reaction inert solvent such as dichloromethane or THF, preferably dichloromethane, at a temperature from about 0°C to about 60°C, preferably at about 25°C.

Compounds of the formula III may also be converted into compounds of the formula I having the same stereochemistry by reacting them with the appropriate compound of the formula



wherein L is defined as above or is imidazole, and then reducing the resulting amide. This reaction is typically carried out in an inert solvent such as THF or dichloromethane at a temperature from about -20°C to about 60°C, preferably in dichloromethane at about 0°C. Reduction of the resulting amide is accomplished by treatment with a reducing agent such as borane dimethylsulfide complex, lithium aluminum hydride or diisobutylaluminum hydride in an inert solvent such as ethyl ether or THF. The reaction temperature may range from about 0°C to about the reflux temperature of the solvent. Preferably, the reduction is accomplished using borane dimethylsulfide complex in THF at about 60°C.

The novel compounds of the formula I and the pharmaceutically acceptable salts thereof are useful as substance P antagonists, i.e., they possess the ability to antagonize the effects of substance P at its receptor site in mammals, and therefore they are able to function as therapeutic agents in the treatment of the aforementioned disorders and diseases in an afflicted mammal.

-13-

The compounds of the formula I which are basic in nature are capable of forming a wide variety of different salts with various inorganic and organic acids. Although such salts must be pharmaceutically acceptable for administration to animals, it is often desirable in practice to initially isolate a compound of the Formula I from the reaction mixture as a pharmaceutically unacceptable salt and then simply convert the latter back to the free base compound by treatment with an alkaline reagent and subsequently convert the latter free base to a pharmaceutically acceptable acid addition salt. The acid addition salts of the base compounds of this invention are readily prepared by treating the base compound with a substantially equivalent amount of the chosen mineral or organic acid in an aqueous solvent medium or in a suitable organic solvent, such as methanol or ethanol. Upon careful evaporation of the solvent, the desired solid salt is readily obtained.

Those compounds of the formula I which are also acidic in nature are capable of forming base salts with various pharmacologically acceptable cations. Examples of such salts include the alkali metal or alkaline-earth metal salts and particularly, the sodium and potassium salts. These salts are all prepared by conventional techniques. The chemical bases which are used as reagents to prepare the pharmaceutically acceptable base salts of this invention are those which form non-toxic base salts with the acidic compounds of formulae I, II and III. Such non-toxic base salts include those derived from such pharmacologically acceptable cations as sodium, potassium calcium and magnesium, etc. These salts can easily be prepared by treating the corresponding acidic compounds with an aqueous solution containing the desired pharmacologically acceptable cations, and then evaporating the resulting solution to dryness, preferably under reduced pressure. Alternatively, they may also be prepared by mixing lower alkanolic solutions of the acidic compounds and the desired alkali

-14-

metal alkoxide together, and then evaporating the resulting solution to dryness in the same manner as before. In either case, stoichiometric quantities of reagents are preferably employed in order to ensure completeness of reaction and maximum product of yields of the desired final product.

The compounds of Formula I and their pharmaceutically acceptable salts exhibit substance P receptor binding activity and therefore are of value in the treatment and prevention of a wide variety of clinical conditions the treatment or prevention of which are effected or facilitated by a decrease in substance P mediated neurotransmission. Such conditions include inflammatory diseases (e.g., arthritis, psoriasis, asthma and inflammatory bowel disease), anxiety, depression or dysthymic disorders, colitis, psychosis, pain, allergies such as eczema and rhinitis, chronic obstructive airways disease, hypersensitivity disorders such as poison ivy, hypertension, vasospastic diseases such as angina, migraine and Reynaud's disease, fibrosing and collagen diseases such as scleroderma and eosinophilic fascioliasis, reflex sympathetic dystrophy such as shoulder/hand syndrome, addiction disorders such as alcoholism, stress related somatic disorders, peripheral neuropathy, neuralgia, neuropathological disorders such as Alzheimer's disease, AIDS related dementia, diabetic neuropathy and multiple sclerosis, disorders related to immune enhancement or suppression such as systemic lupus erythematosus, and rheumatic diseases such as fibrositis. Hence, these compounds are readily adapted to therapeutic use as substance P antagonists for the control and/or treatment of any of the aforesaid clinical conditions in mammals, including humans.

The compounds of the formula I and the pharmaceutically acceptable salts thereof can be administered via either the oral, parenteral or topical routes. In general, these compounds are most desirably administered in dosages ranging from about 0.5 mg to about 500 mg per day, although variations will necessarily occur depending upon the weight

-15-

and condition of the subject being treated and the particular route of administration chosen. Variations may occur depending upon the species of animal being treated and its individual response to said medicament, as well as on
5 the type of pharmaceutical formulation chosen and the time period and interval at which such administration is carried out. In some instances, dosage levels below the lower limit of the aforesaid range may be more than adequate, while in other cases still larger doses may be employed without
10 causing any harmful side effect, provided that such larger doses are first divided into several small doses for administration throughout the day.

The compounds of the invention may be administered alone or in combination with pharmaceutically acceptable
15 carriers or diluents by either of the three routes previously indicated, and such administration may be carried out in single or multiple doses. More particularly, the novel therapeutic agents of this invention can be administered in a wide variety of different dosage forms,
20 i.e., they may be combined with various pharmaceutically acceptable inert carriers in the form of tablets, capsules, lozenges, troches, hard candies, powders, sprays, creams, salves, suppositories, jellies, gels, pastes, lotions, ointments, aqueous suspensions, injectable solutions,
25 elixirs, syrups, and the like. Such carriers include solid diluents or fillers, sterile aqueous media and various non-toxic organic solvents, etc. Moreover, oral pharmaceutical compositions can be suitably sweetened and/or flavored. In general, the therapeutically-effective
30 compounds of this invention are present in such dosage forms at concentration levels ranging from about 5.0% to about 70% by weight.

For oral administration, tablets containing various excipients such as microcrystalline cellulose, sodium
35 citrate, calcium carbonate, dicalcium phosphate and glycine may be employed along with various disintegrants such as starch (and preferably corn, potato or tapioca starch),

-16-

alginic acid and certain complex silicates, together with granulation binders like polyvinylpyrrolidone, sucrose, gelatin and acacia. Additionally, lubricating agents such as magnesium stearate, sodium lauryl sulfate and talc are often very useful for tableting purposes. Solid compositions of a similar type may also be employed as fillers in gelatin capsules; preferred materials in this connection also include lactose or milk sugar as well as high molecular weight polyethylene glycols. When aqueous suspensions and/or elixirs are desired for oral administration, the active ingredient may be combined with various sweetening or flavoring agents, coloring matter or dyes, and, if so desired, emulsifying and/or suspending agents as well, together with such diluents as water, ethanol, propylene glycol, glycerin and various like combinations thereof.

For parenteral administration, solutions of a therapeutic compound of the present invention in either sesame or peanut oil or in aqueous propylene glycol may be employed. The aqueous solutions should be suitably buffered (preferably pH greater than 8) if necessary and the liquid diluent first rendered isotonic. These aqueous solutions are suitable for intravenous injection purposes. The oily solutions are suitable for intraarticular, intramuscular and subcutaneous injection purposes. The preparation of all these solutions under sterile conditions is readily accomplished by standard pharmaceutical techniques well known to those skilled in the art.

Additionally, it is also possible to administer the compounds of the present invention topically when treating inflammatory conditions of the skin and this may preferably be done by way of creams, jellies, gels, pastes, ointments and the like, in accordance with standard pharmaceutical practice.

The activity of the compounds of the present invention as substance P antagonists is determined by their ability to inhibit the binding of substance P at its receptor sites in

-17-

bovine caudate tissue, employing radioactive ligands to visualize the tachykinin receptors by means of autoradiography. The substance P antagonizing activity of the herein described compounds may be evaluated by using the standard assay procedure described by M. A. Cascieri et al., as reported in the Journal of Biological Chemistry, Vol. 258, p. 5158 (1983). This method essentially involves determining the concentration of the individual compound required to reduce by 50% the amount of radiolabelled substance P ligands at their receptor sites in said isolated cow tissues, thereby affording characteristic IC_{50} values for each compound tested.

In this procedure, bovine caudate tissue is removed from a $-70^{\circ}C$ freezer and homogenized in 50 volumes (w./v.) of an ice-cold 50 mM Tris (i.e., trimethamine which is 2-amino-2-hydroxymethyl-1,3-propanediol) hydrochloride buffer having a pH of 7.7. The homogenate is centrifuged at $30,000 \times G$ for a period of 20 minutes. The pellet is resuspended in 50 volumes of Tris buffer, rehomogenized and then recentrifuged at $30,000 \times G$ for another twenty-minute period. The pellet is then resuspended in 40 volumes of ice-cold 50 mM Tris buffer (pH 7.7) containing 2 mM of calcium chloride, 2 mM of magnesium chloride, 40 g/ml of bacitracin, $4\mu g/ml$ of leupeptin, $2\mu g$ of chymostatin and 200 g/ml of bovine serum albumin. This step completes the production of the tissue preparation.

The radioligand binding procedure is then carried out in the following manner, viz., by initiating the reaction via the addition of 100 μl of the test compound made up to a concentration of 1 μM , followed by the addition of 100 μl of radioactive ligand made up to a final concentration 0.5 mM and then finally by the addition of 800 μl of the tissue preparation produced as described above. The final volume is thus 1.0 ml, and the reaction mixture is next vortexed and incubated at room temperature (ca. $20^{\circ}C$) for a period of 20 minutes. The tubes are then filtered using a cell harvester, and the glass fiber filters (Whatman

-18-

GF/B) are washed four times with 50 mM of Tris buffer (pH 7.7), with the filters having previously been presoaked for a period of two hours prior to the filtering procedure. Radioactivity is then determined in a Beta counter at 53% counting efficiency, and the IC₅₀ values are calculated by using standard statistical methods.

The anti-psychotic activity of the compounds of the present invention as neuroleptic agents for the control of various psychotic disorders is determined primarily by a study of their ability to suppress substance P-induced or substance P agonist induced hypermotility in guinea pigs. This study is carried out by first dosing the guinea pigs with a control compound or with an appropriate test compound of the present invention, then injecting the guinea pigs with substance P or a substance P agonist by intracerebral administration via canula and thereafter measuring their individual locomotor response to said stimulus.

The present invention is illustrated by the following examples. It will be understood, however, that the invention is not limited to the specific details of these examples.

Example 1

(2S,3S)-N-(5-isopropyl-2-methoxyphenyl)methyl-2-diphenylmethyl-1-azabicyclo[2.2.2]octan-3-amine
methanesulfonic acid salt

A. (2S,3S)-2-(2-diphenylmethyl-1-azabicyclo[2.2.2]octan-3-amine

(2S,3S)-N-(2-methoxyphenyl)methyl-1-azabicyclo[2.2.2]octan-3-amine (4.12 g, 10 mmol) was hydrogenated at room temperature in methanol (MeOH) (40 ml)/6N hydrochloric acid (HCl) (10 ml) by using 20% palladium hydroxide on carbon (0.2 g) at 2.5 kg/cm² of hydrogen for 60 hours. The reaction was filtered and the filtrate was concentrated to give the crude product, which was crystallized from ethanol.

-19-

B. (2S,3S)-N-(5-isopropyl-2-methoxyphenyl)methyl-2-diphenylmethyl-1-azabicyclo[2.2.2]octan-3-amine methanesulfonic acid salt

To a solution of a 5-isopropyl-2-methoxybenzaldehyde
5 (748 mg, 4.2 mmol) and (2S,3S)-2-diphenylmethyl-1-azabi-
cyclo[2.2.2]octan-3-amine (4 mmol) in methylene chloride
(CH₂Cl₂) (40 ml) was added in portions triacetoxyborohydride
(933 mg, 4.4 mmol). The mixture was stirred until the amine
disappeared. The solution was carefully neutralized with an
10 ice-cooled saturated sodium bicarbonate (NaHCO₃) solution.
The organic layer was washed with water, dried over
magnesium sulfate (MgSO₄), and concentrated to give the
product (1.82 g). To a solution of the product in acetone
was added equivalent methansulfonate acid. Then the
15 precipitated mesylate salt was collected and dried under
vacuum.

The title compounds of Examples 2-15 were prepared by
a procedure similar to that of Example 1.

Example 2

20 (2S,3S)-N-(5-methyl-2-methoxyphenyl)methyl-2-diphenyl-
methyl-1-azabicyclo[2.2.2]octan-3-amine methanesulfonic acid
salt

M.p.: 240°C.

IR (KBr) cm⁻¹: 3410, 2980, 1640, 1500, 1455, 1200, 1060,
25 710.

¹H NMR (CDCl₃) δ: 7.5-7.2 (10H, m), 7.10 (1H, m) 8.40
(1H, br), 6.63 (1H, d, J=8Hz), 6.39 (1H, br s), 4.55 (1H, m)
4.12 (1H, m), 3.80-3.30 (5H, m), 3.53 (3H, s), 3.25 (1H, m),
3.20 (1H, m), 2.47 (3H, s), 2.42 (1H, m), 2.21 (3H, s),
30 2.30-2.16 (4H, m).

Example 3

(2S,3S)-N-(5-ethyl-2-methoxyphenyl)methyl-2-diphenyl-
methyl-1-azabicyclo[2.2.2]octan-3-amine methanesulfonic acid
salt

35 M.p.: 151°C.

IR (KBr) cm⁻¹: 3420, 2970, 1640, 1510, 1460, 1195, 1060,
785.

-20-

¹H NMR (CDCl₃) δ: 10.9 (1H, br), 8.18 (1H, br) 7.85-7.15 (11H, m), 6.86 (1H, m), 6.68 (1H, d, J=8.8Hz), 5.57 (1H, br) 5.45 (1H, m) 5.05 (1H, d, J=13.2Hz), 4.24-3.65 (5H, m), 3.48 (3H, s), 3.50-3.35 (3H, m), 2.92 (1H, m), 2.61 (6H, s), 2.8-2.2 (6H, m), 2.54 (2H, m), 2.30-1.80 (2H, m), 1.21 (3H, m).

Example 4

(2S,3S)-N-(5-isopropyl-2-methoxyphenyl)methyl-2-diphenylmethyl-1-azabicyclo[2.2.2]octan-3-amine
10 methanesulfonic acid salt

M.p.: 221°C.

IR (KBr) cm⁻¹: 3430, 2960, 1600, 1500, 1455, 1245, 1160, 1040, 710.

¹H NMR (CDCl₃) δ: 8.40 (1H, br) 7.5-7.2 (10H, m) 7.06 (1H, m), 6.67 (1H, d, J=8.4Hz), 6.56 (1H, br, s) 4.58 (1H, m) 4.24 (1H, m), 3.6-3.3 (5H, m), 3.53 (3H, s), 3.24 (1H, m), 3.22 (1H, m), 2.78 (1H, sep, J=7Hz), 2.48 (4H, s), 2.42 (1H, m), 2.27 (1H, m), 1.99 (2H, m), 1.76 (1H, m), 1.20 (6H, dd, J=2.9Hz, 7Hz).

20

Example 5

(2S,3S)-N-(5-sec-butyl-2-methoxyphenyl)methyl-2-diphenylmethyl-1-azabicyclo[2.2.2]octan-3-amine
methanesulfonic acid salt

M.p.: 224°C.

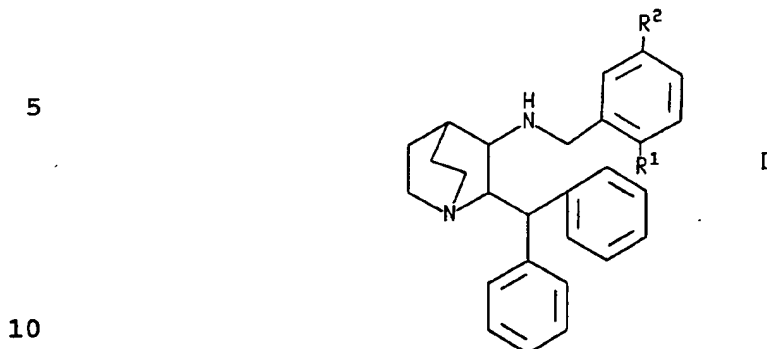
25 IR (KBr) cm⁻¹: 3440, 2960, 1610, 1500, 1455, 1220, 1160, 1035, 755, 710, 560.

¹H NMR (CDCl₃) δ: 8.41 (1H, br), 7.5-7.2 (10H, m) 7.00 (1H, m), 6.67 (1H, d, J=8.4Hz), 6.52 (1H, br, s) 4.58 (1H, d, J=11.7Hz), 4.25 (1H, m), 3.70-3.35 (5H, m), 3.53 (3H, s), 30 3.21 (2H, m), 2.46 (3H, s), 2.43 (1H, m), 2.26 (1H, m), 2.04 (1H, m), 2.00-1.60 (3H, m), 1.52 (2H, m), 1.18 (2H, m), 0.82 (3H, m).

-21-

CLAIMS

1. A compound of the formula



wherein R^1 is methoxy and R^2 is selected from isopropyl, tert-butyl, methyl, ethyl and sec-butyl; or a pharmaceutically acceptable salt of such compound.

15 2. A compound according to claim 1, wherein said compound is selected from the group consisting of:

(2S,3S)-N-(5-isopropyl-2-methoxyphenyl)methyl-2-diphenylmethyl-1-azabicyclo[2.2.2]octan-3-amine;

20 (2S,3S)-N-(5-ethyl-2-methoxyphenyl)methyl-2-diphenylmethyl-1-azabicyclo[2.2.2]octan-3-amine;

(2S,3S)-N-(5-isopropyl-2-methoxyphenyl)methyl-2-diphenylmethyl-1-azabicyclo[2.2.2]octan-3-amine;

(2S,3S)-N-(5-methyl-2-methoxyphenyl)methyl-2-diphenylmethyl-1-azabicyclo[2.2.2]octan-3-amine;

25 (2S,3S)-N-(5-tert-butyl-2-methoxyphenyl)methyl-2-diphenylmethyl-1-azabicyclo[2.2.2]octan-3-amine; and

(2S,3S)-N-(5-sec-butyl-2-methoxyphenyl)methyl-2-diphenylmethyl-1-azabicyclo[2.2.2]octan-3-amine;

30 and the pharmaceutically acceptable salts of such compounds.

3. (2S,3S)-N-(5-isopropyl-2-methoxyphenyl)methyl-2-diphenylmethyl-1-azabicyclo[2.2.2]octan-3-amine methansulfonate.

35 4. A pharmaceutical composition for treating or preventing a condition selected from the group consisting of inflammatory diseases, anxiety, colitis, depression or dysthymic disorders, psychosis, pain, allergies, chronic

-22-

obstructive airways disease, hypersensitivity disorders, hypertension, vasospastic diseases, fibrosing and collagen diseases, reflex sympathetic dystrophy, addiction disorders, stress related somatic disorders, peripheral neuropathy, neuralgia, neuropathological disorders, disorders related to immune enhancement or suppression and rheumatic diseases in a mammal, comprising an amount of a compound according to claims 1 effective in preventing or treating such condition and a pharmaceutically acceptable carrier.

5 5. A method of treating or preventing a condition selected from the group consisting of inflammatory diseases anxiety, colitis, depression or dysthymic disorders, psychosis, pain, allergies, chronic obstructive airways disease, hypersensitivity disorders, hypertension, vasospastic diseases, fibrosing and collagen diseases, reflex sympathetic dystrophy, addiction disorders, stress related somatic disorders, peripheral neuropathy, neuralgia, neuropathological disorders, disorders related to immune enhancement or suppression and rheumatic diseases in a mammal, comprising administering to a mammal in need of such treatment or prevention an amount of a compound according to claim 1 effective in preventing or treating such condition.

15 6. A pharmaceutical composition for antagonizing the effects of substance P in a mammal, comprising a substance P antagonizing effective amount of a compound according to claim 1 and a pharmaceutically acceptable carrier.

25 7. A method of antagonizing the effects of substance P in a mammal, comprising administering to said mammal a substance P antagonizing effective amount of a compound according to claim 1.

30 8. A pharmaceutical composition for treating or preventing a condition in a mammal, the treatment or prevention of which is effected or facilitated by a decrease in substance P mediated neurotransmission, comprising an amount of a compound according to claim 1 effective in antagonizing the effect of substance P at its receptor site and a pharmaceutically acceptable carrier.

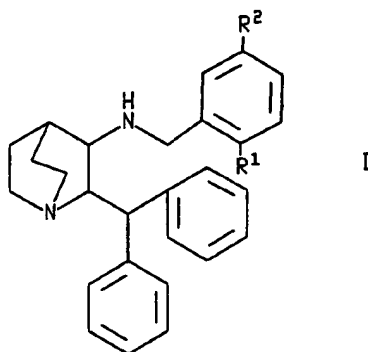
-23-

9. A method of treating or preventing a condition in a mammal, the treatment or prevention of which is effected or facilitated by a decrease in substance P mediated neurotransmission, comprising administering to a mammal in need of such treatment or prevention an amount of a compound according to claim 1, or a pharmaceutically acceptable salt thereof, effective in antagonizing the effect of substance P at its receptor site.

10. A pharmaceutical composition for treating or preventing a condition in a mammal, the treatment or prevention of which is effected or facilitated by a decrease in substance P mediated neurotransmission, comprising an amount of a compound according to claim 1, or a pharmaceutically acceptable salt thereof, effective in treating or preventing such condition and a pharmaceutically acceptable carrier.

11. A method of treating or preventing a condition in mammal, the treatment or prevention of which is effected or facilitated by a decrease in substance P mediated neurotransmission, comprising administering to a mammal in need of such treatment or prevention an amount of a compound according to claim 1 effective in treating or preventing such condition.

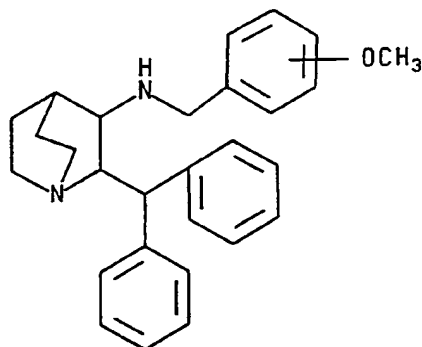
12. A process for preparing a compound of the formula



wherein R¹ is methoxy and R² is independently selected from isopropyl, tert-butyl, methyl, ethyl and sec-butyl, or a pharmaceutically acceptable salt of such compound, comprising subjecting a compound of the formula

-24-

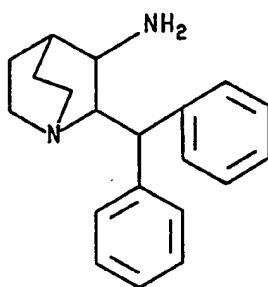
5



II

10 having the same stereochemistry as the desired compound of formula III, to hydrolytic or hydrogenolytic removal of the methoxybenzyl group to produce the corresponding compound of the formula

15

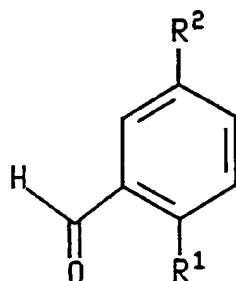


III

20

having the same stereochemistry, and then reacting the compound of formula III so formed with an aldehyde of the formula

25



IV

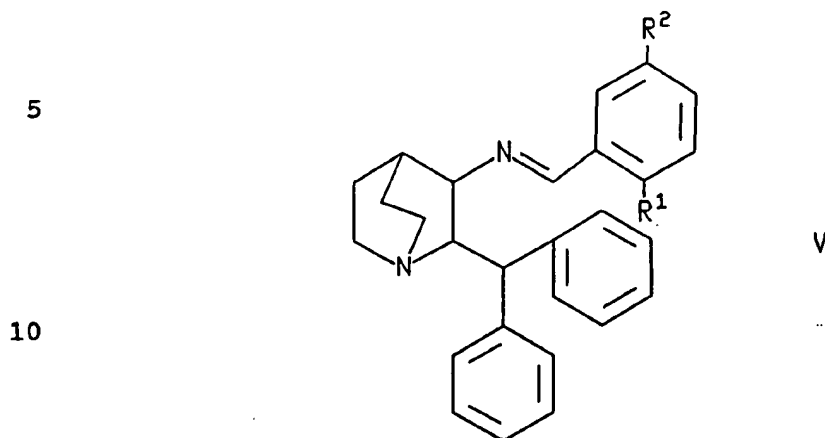
30

in the presence of a reducing agent.

13. A process according to claim 12, wherein the
35 reaction between compounds of the formulae III and IV, as defined in claim 12, is carried out in the presence of a drying agent or using an apparatus designed to remove

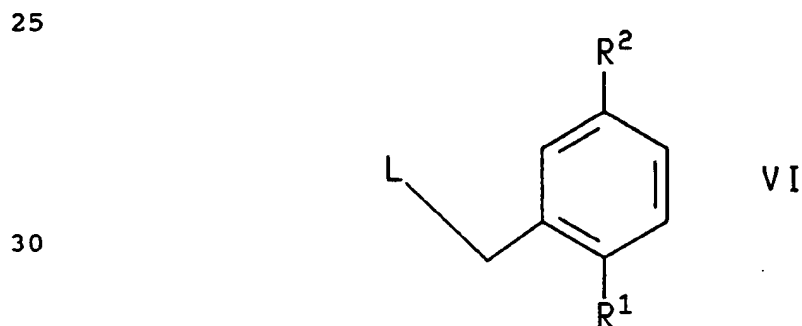
-25-

azeotropically the water generated to produce an imine of the formula



and then reacting the imine of formula V with a reducing agent.

14. A process for preparing a compound of the formula I, as defined in claim 12, comprising subjecting a compound of the formula II, as defined in claim 12, having the same stereochemistry as the desired compound of formula I, to hydrolytic removal of the methoxybenzyl group to produce a compound of the formula III, as defined in claim 12, having the same stereochemistry as the desired compound of formula I, and reacting the compound of formula III so formed with a compound of the formula

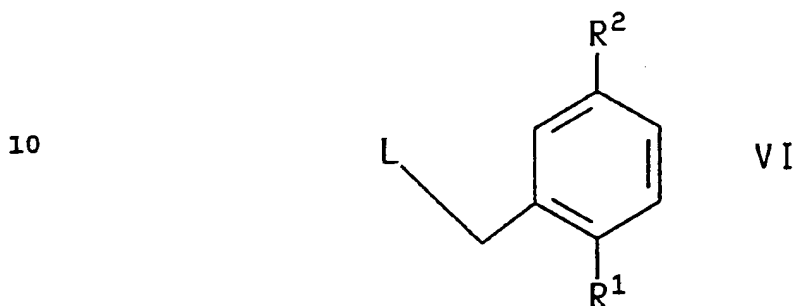


wherein L is a leaving group.

15. A process for preparing a compound of the formula I, as defined in claim 12, comprising subjecting a compound of the formula II, as defined in claim 12, having the same

-26-

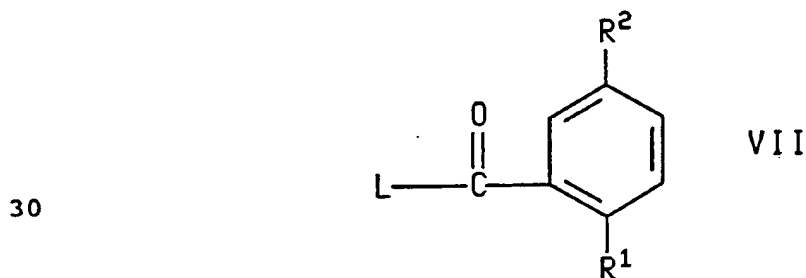
stereochemistry as the desired compound of formula I, to
hydrogenolytic removal of the methoxybenzyl group to produce
a compound of the formula III, as defined in claim 12,
having the same stereochemistry as the desired compound of
5 formula I, and reacting the compound of formula III so
formed with a compound of the formula



15

wherein L is a leaving group.

16. A process for preparing a compound of the formula
I, as defined in claim 12, comprising subjecting a compound
of the formula II, as defined in claim 12, having the same
20 stereochemistry as the desired compound of formula I, to
hydrolytic removal of the methoxybenzyl group to produce a
compound of the formula III, as defined in claim 12, having
the same stereochemistry as the desired compound of formula
I, and reacting the compound of formula III so formed with
25 a compound of the formula

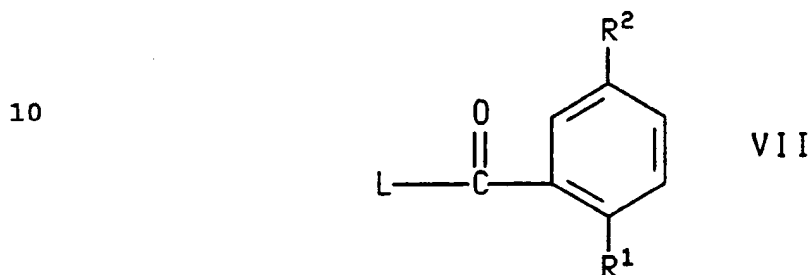


wherein L is a leaving group or imidazole, and then reducing
35 the resulting amide.

17. A process for preparing a compound of the formula
I, as defined in claim 12, comprising subjecting a compound

-27-

of the formula II, as defined in claim 12, having the same stereochemistry as the desired compound of formula I, to hydrogenolytic removal of the methoxybenzyl group to produce a compound of the formula III, as defined in claim 12, having the same stereochemistry as the desired compound of formula I, and reacting the compound of formula III so formed with a compound of the formula



15

wherein L is a leaving group or imidazole, and then reducing the resulting amide.

18. A process according to any of claims 12-17, further comprising converting the compound of formula I formed thereby into a pharmaceutically acceptable salt of such compound.

19. A process according to any of claims 12-18, wherein the compound prepared by said process is a compound selected from the group consisting of:

25 (2S,3S)-N-(5-isopropyl-2-methoxyphenyl)methyl-2-diphenylmethyl-1-azabicyclo[2.2.2]octan-3-amine;

(2S,3S)-N-(5-methyl-2-methoxyphenyl)methyl-2-diphenylmethyl-1-azabicyclo[2.2.2]octan-3-amine;

30 (2S,3S)-N-(5-ethyl-2-methoxyphenyl)methyl-2-diphenylmethyl-1-azabicyclo[2.2.2]octan-3-amine;

(2S,3S)-N-(5-isopropyl-2-methoxyphenyl)methyl-2-diphenylmethyl-1-azabicyclo[2.2.2]octan-3-amine;

(2S,3S)-N-(5-tert-butyl-2-methoxyphenyl)methyl-2-diphenylmethyl-1-azabicyclo[2.2.2]octan-3-amine;

35 (2S,3S)-N-(5-sec-butyl-2-methoxyphenyl)methyl-2-diphenylmethyl-1-azabicyclo[2.2.2]octan-3-amine;

-28-

and the pharmaceutically acceptable salts of such compounds.

20. A process according to claim 18, wherein the compound prepared by said process is (2S, 3S)-N-(5-isopropyl-2-methoxyphenyl)methyl-2-diphenylmethyl-1-azabicyclo[2.2.2]octan-3-amine methansulfonate.

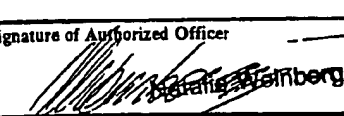
21. A process according to claim 18, wherein the compound prepared by said process is (2S, 3S)-N-(5-isopropyl-2-methoxyphenyl)methyl-2-diphenylmethyl-1-azabicyclo[2.2.2]octan-3-amine dihydrochloride.

22. (2S, 3S)-N-(5-isopropyl-2-methoxyphenyl)methyl-2-diphenylmethyl-1-azabicyclo[2.2.2]octan-3-amine dihydrochloride.

INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 92/03317

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) ⁶		
According to International Patent Classification (IPC) or to both National Classification and IPC Int.C1.5 C 07 D 453/02 A 61 K 31/435		
II. FIELDS SEARCHED		
Minimum Documentation Searched ⁷		
Classification System	Classification Symbols	
Int.C1.5	C 07 D A 61 K	
Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched ⁸		
III. DOCUMENTS CONSIDERED TO BE RELEVANT⁹		
Category ^o	Citation of Document, ¹¹ with indication, where appropriate, of the relevant passages ¹²	Relevant to Claim No. ¹³
1 X	WO,A,9005729 (PFIZER) 31 May 1990, see claims 1,37; example 22 (cited in the application) -----	1,4
<div style="display: flex; justify-content: space-between;"> <div style="width: 45%;"> <p>^o Special categories of cited documents : ¹⁰</p> <p>"A" document defining the general state of the art which is not considered to be of particular relevance</p> <p>"E" earlier document but published on or after the international filing date</p> <p>"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)</p> <p>"O" document referring to an oral disclosure, use, exhibition or other means</p> <p>"P" document published prior to the international filing date but later than the priority date claimed</p> </div> <div style="width: 45%;"> <p>"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention</p> <p>"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step</p> <p>"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.</p> <p>"&" document member of the same patent family</p> </div> </div>		
IV. CERTIFICATION		
Date of the Actual Completion of the International Search		Date of Mailing of this International Search Report
10-09-1992		14. 10. 92
International Searching Authority		Signature of Authorized Officer
EUROPEAN PATENT OFFICE		

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 92/03317

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
Remark: Although claims 5,7,9 and 11 are directed to a method of treatment of (diagnostic method practised on) the human/animal body the search has been carried out and based on the alleged effects of the compound/ composition.
2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

US 9203317
SA 60522

EPO FORM P0479

For more details about this annex : see Official Journal of the European Patent Office, No. 12/82